GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole rejection of record in this case is a rejection of all of the claims (claims 1, 17-19) as being unpatentable over Yongan (1996) [note the examiner erroneously indicated a date of 1966] in view of Yongan (1998) and Ellis under 35 USC 103(a). The examiner states that Yongan (1998) refers to the Yongan (1996) thesis, which identifies the protein Fip-2, which can utilize interaction with induced cellular factors to activate apoptosis. The examiner recognizes that neither Yongan reference teaches anti-Fip-2 antibodies. However, the examiner states that it would have been obvious to raise antibodies directed to Fip-2 with a reasonable expectation of success. The motivation to do so would have been in order to study the interaction of Fip-2 with the cellular proteins involved in TNF-α induced apoptosis.

The examiner states that the present specification teaches that the leucine zipper domains and the C-terminus of RAP-2 encoded by SEQ ID NO:4 and Fip-2 are conserved. Thus, the examiner concludes that anti-Fip-2 antibodies recognizing these domains would necessarily be specific for RAP-2, thereby meeting the terms of claim 1. The examiner relies on Ellis as teaching that monoclonal and chimeric antibodies and detectable labels are known in the prior art and that one of ordinary skill in the art would have been motivated to use a monoclonal antibody in order to study the function of specific domains in Fip-2 function or to use a humanized antibody that

could be used in therapy for humans or to use a label in order to localize the protein inside the cell.

In response to applicant's arguments, the examiner stated that the fact that the overlapping regions between RAP-2 and Fip-2 are small and therefore a large percentage of monoclonal antibodies raised against Fip-2 would not bind to RAP-2 is irrelevant as the present claims encompass antibodies against the overlapping regions and the combined teaching of the prior art provide motivation to make such an antibody and therefore renders the invention *prima facie* obvious.

In the advisory action, the examiner stated that the present claims do not recite that the antibody recognizes RAP-2 without recognizing Fip-2 and that the claims are drawn to a composition and not to a method of screening. The examiner states that the prior art cited teaches anti-Fip-2 antibodies and since Fip-2 and RAP-2 sequences overlap, such antibodies would necessarily comprise antibodies capable of recognizing RAP-2.

ARGUMENTS

THE REJECTION UNDER 35 USC 103

The arguments directed to claim 1 are applicable to claim 1 and all claims dependent therefrom. A separate argument will be presented as to why claims 17 and 18, as a group, are also independently patentable.

The Subgenus of Antibodies Within the Scope of Claim 1 Would not have been Obvious from the Genus of Antibodies Allegedly Made Obvious by the Combined Teachings of the Prior Art.

It is essentially the examiner's position that it would have been obvious to raise antibodies against Fip-2 and that among the antibodies that could be raised against Fip-2 are antibodies that will also bind RAP-2 and would thus fall within the scope of claim 1. Thus, the examiner concludes that the subject matter of claim 1 is *prima facie* obvious and unpatentable under 35 USC 103. While applicants will argue below that the examiner has not established a *prima facie* case that antibodies can be raised against Fip-2 that will also bind RAP-2, for the purpose of the present argument, applicant will concede that the examiner has established this. However, even if such antibodies exist, the subgenus (or subset) of the antibodies encompassed by claim 1 possess a property that would have been totally unexpected from the genus (or set) of antibodies allegedly made obvious by the combined teachings of the prior art. Hence, the claimed antibodies are unobvious.

That a genus may be obvious does not necessarily make obvious every species within that genus. At best, the examiner alleges that the genus of anti-Fip-2 antibodies is made obvious by the combined teachings of the prior art. However, the present claims are not directed to such a genus and would not be anticipated if such a genus were part of the prior art. The present claims are effectively species or subgenus claims directed to that relatively small subset (if it exists at all) of the prior art genus of anti-Fip-2 antibodies that will also bind to RAP-2.

The antibodies that are allegedly *prima facie* obvious from the combined teachings of the prior art would all bind to Fip-2. Because Fip-2 has large areas that are not homologous to RAP-2 (see the sequence alignment of Figure 3(B), discussed below), it would not be expected that every antibody raised against Fip-2 will necessarily bind RAP-2. Thus, most of the antibodies allegedly made *prima facie* obvious by the combined teachings of the prior art would not fall within the scope of any of the present claims. This is why the antibodies allegedly made *prima facie* obvious by the combined teachings of the prior art represent a genus of anti-Fip-2 antibodies that include a majority of antibodies that do not bind RAP-2. To the extent that there are any anti-RAP-2 antibodies within this genus, they represent only a species or subgenus thereof. This subgenus is not *per se* obvious from the existence of or obviousness of an genus of antibodies that encompasses them.

Attention is directed to the guidelines of the MPEP at §2144.08 directed to obviousness of species when the prior teaches a genus. Note particularly Section II where it states:

> The patentability of a claim to a specific compound or subgenus embraced by a prior art genus should be analyzed no differently than any other claim for purposes of 35 U.S.C. 103. "The section 103 requirement of unobviousness is no different in chemical cases than with respect to other categories of patentable inventions." *In re Papesch*, 315 F.2d 381, 385, 137 USPQ 43, 47 (CCPA 1963). A determination of patentability under 35 U.S.C. 103 should be made upon the facts of the particular case in view of the totality of the circumstances. See, e.g., *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*in banc*). Use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103. See, e.g., *In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996); *In re Ochiai*, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995); *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). <u>The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness.</u> *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract from *Merck* [*& Co. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d

> 1843 (Fed. Cir. 1989)] the rule that... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."). See also *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995). [Emphasis added]

Accordingly, even if it is determined that the examiner has established a *prima facie* case that the entire genus of anti-Fip-2 antibodies would have been obvious, that does not establish a *prima facie* case of obviousness for every species or subgenus within that genus. See *In re Baird, supra*. The present claims are not directed to the genus of anti-Fip-2 antibodies. The present claims are specifically directed to the subgenus of those anti-Fip-2 antibodies that binds RAP-2.

The examiner has provided no rationale whatsoever why the claimed subgenus of RAP-2 binding antibodies would have been obvious from the genus of anti-Fip-2 antibodies. The examiner seems to assume that there is some kind of a *per se* rule that if she establishes the obviousness of a genus, every species or subgenus thereunder is necessarily obvious. But the above-quoted section of §2144.08 of the MPEP and the cases cited therein establish that there is no such *per se* rule. For this reason alone, the examiner has not met her burden of establishing a *prima facie* case of obviousness for the presently claimed subgenus of the genus of antibodies

allegedly made obvious by the combined teachings of the prior art.

Furthermore, the claimed subject matter could not possibly have been obvious from the genus in view of the fact that the subgenus has properties which are unexpected from any consideration of the properties of the genus. The properties of the claimed subgenus necessarily include, by definition, the property of binding RAP-2. The fact that there may exist a subgenus of antibodies, within the genus of anti-Fip-2 antibodies, that also bind RAP-2, was unknown at the time of the present invention.

Even if the examiner had submitted a rationale to establish a *prima facie* case of obviousness for the presently claimed subgenus of the antibodies of the prior art, such a *prima facie* case of obviousness can be rebutted by a showing of unexpected results. Note MPEP 2145 where it states:

> Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. [*In re*] *Dillon*, [919 F.2d 688, 692-3, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)].

By definition, all of the antibodies within the scope of claim 1 bind RAP-2. If any of the antibodies allegedly made *prima facie* obvious by the combined teachings of the prior art have

the property of binding RAP-2, this would have been an unexpected property at the time of the present invention as the existence of RAP-2 was not known to the prior art at the time of the present invention.

While it would have been expected that any antibody raised against Fip-2 would bind to Fip-2, those antibodies which also bind to RAP-2 possess the unexpected property of being able to bind to RAP-2. It is only by hindsight that the examiner reaches the conclusion that some of the antibodies that can be raised against Fip-2 may bind to RAP-2; but if they do, this is necessarily unexpected as RAP-2 did not exist in the prior art. The fact that some of the antibodies that can be raised against Fip-2 can be used to fish RAP-2 out of a mixture of proteins, could not possibly have been expected at the time of the present invention as the existence of RAP-2 was not known. Thus, the subset of anti-Fip-2 antibodies that also bind to RAP-2 (assuming that such a subset even exists) would not have been obvious since one of ordinary skill in the art would have no way to identify any antibody that falls within this subset that binds to RAP-2, as RAP-2 is not part of the prior art.

In the Advisory Action, the examiner states that the present claims do not recite that the antibody recognizes RAP-2 without recognizing Fip-2. This is correct and there is a

good reason for this: it does not matter whether any of the antibodies of the present invention recognize Fip-2. The present claims do not intend to exclude antibodies that recognize Fip-2. It is only necessary that the present claims cover antibodies that recognize RAP-2. If any of such antibodies also recognize Fip-2, that is irrelevant to the scope of claim 1. Moreover, that fact does not affect the patentability of those antibodies for the reasons discussed above. As discussed above, the prior art does not make obvious any of the specific antibodies allegedly made obvious by the combined teachings of the prior art which happen to recognize RAP-2. Those are the only antibodies covered by the present claims.

Accordingly, considering all of the evidence of record, a person of ordinary skill in the art would not have considered a claim to the subgenus of anti-RAP-2 antibodies to have been obvious from any reading of Yongan 1996, Yongan 1998 and Ellis. Reversal of the examiner and withdrawal of the rejection of claim 1 and those claims dependent therefrom for this reason is therefore respectfully urged.

It Is Not *Prima Facie* Obvious That Any Antibody That Can Be Raised Against Fip-2 Will Necessarily Bind to Rap-2

The examiner has stated in the Official Action of July 26, 2007:

> It is noted that the specification teaches that the leucine zipper domains and the C-terminus of Rap-2 (encoded by SEQ ID NO. 4) and Fip-2 are conserved (p. 14, paragraph 0019 and p. 15, paragraph 0021) and therefore anti-Fip-2 antibodies recognizing these domains would necessarily be specific for Rap-2 (claim 1).

Paragraph [0019] referred to by the examiner states that the global alignment of the amino acid sequences of RAP-2 and Fip-2 are shown in Figure 3. Paragraph [0088] clarifies that the alignment of the sequence of Fip-2 and the sequence of RAP-2 (SEQ ID NO: 4) appears in Figure 3B. Thus, it is not necessary to rely on the characterizations in paragraphs [0019] and [0021], as done by the examiner, as one can actually see what is identical and what is preserved in Figure 3B. It can be seen from a review of Figure 3B that the only area of sequence identity of greater than 5 amino acids between RAP-2 and Fip-2 is the 8 amino acid region from amino acid 408 to 415 of RAP-2 and amino acid 566 to 573 of Fip-2.

The examiner is essentially taking the position that at least one antibody that can be raised against Fip-2 would inherently bind to RAP-2. However, the examiner has not satisfied her burden of establishing that such inherency is necessarily the case. Thus, even if this were an anticipation reference and one of the primary references disclosed making antibodies against Fip-2, such a rejection based on inherency

must fall as the examiner cannot establish that such inherency is inevitable and certain. Note *In re Oelrich*, 212 USPQ 323, 326 (CCPA 1981), where it states:

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

It is possible that amino acids 566-573 of Fip-2 are immunogenic and will cause an antibody to be raised against them. However, it is also possible that this sequence is not exposed on the surface of the Fip-2 protein and therefore would not generate an antibody specific thereto when using Fip-2 as an immunogen. Furthermore, even if it were possible to raise an antibody that recognizes amino acids 566-573 of Fip-2, it is possible that such an antibody would not bind to the same sequence that is part of RAP-2. It is also possible that, although the amino acids are the same, the amino acids are on the surface of Fip-2 but not necessarily on the surface of RAP-2, in which case the antibody raised against Fip-2 would not recognize the same sequence that is hidden in RAP-2. It is not sufficient that a certain thing <u>may</u> result from a given set of circumstances to establish inherency, it must be inevitable.

See also MPEP §2112 IV which states:

> Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.

Here, the examiner is presenting nothing more than an invitation to investigate whether it is possible to raise an antibody against Fip-2 that would bind to RAP-2. In view of the only sporadic homology between RAP-2 and Fip-2, as can be clearly seen in Figure 3(B) of the present specification, the examiner has not established that there is certainty that any antibody raised against Fip-2 would necessarily bind to RAP-2.

Accordingly, the examiner has not satisfied her burden of establishing a *prima facie* case that the combined teachings of the prior art would necessarily include any antibodies that would bind to RAP-2. One of ordinary skill in the art would not consider that antibodies raised against Fip-2 as an immunogen would necessarily produce anti-Fip-2 antibodies that would necessarily recognize a domain which

also appears on RAP-2 or that such antibodies, even if they were raised, would necessarily be specific for RAP-2.

Accordingly, the examiner has not established a *prima facie* case of obviousness. Reversal of the examiner and allowance of all of claims 1 and 17 to 19 is therefore warranted for this reason alone.

Claims 17 and 18 Are Patentable In Their Own Right As Monoclonal Antibodies, Or Fragments Thereof, Would Not Have Been Obvious From the Combined Teachings of the Prior Art.

Claim 17 is drawn to monoclonal antibodies or fragments of monoclonal antibodies. Those of ordinary skill in the art would understand that in any given round of hybridoma production, there is no guarantee that any of the monoclonal antibodies that are obtained by screening against Fip-2 would necessarily be directed to that portion of Fip-2 that happens to overlap with RAP-2 (assuming that any such antibodies even exist). It is not inherent that any such monoclonal antibodies would be obtained. Certainly, those of ordinary skill in art understand that it is common practice in the antibody art that antibodies that are not found in one round of hybridomas may be found in another. In any event, those of ordinary skill in art would never know whether any given hybridoma found by the combination of references suggested by the examiner would fall within the scope of the

present claims. This does not even establish a *prima facie* case of obviousness.

The examiner has not discussed whether the regions of overlap are particularly immunogenic. One cannot simply assume that monoclonal antibodies can be raised against every possible region of a protein. Some regions may be folded within the protein or be obscured. Thus, there is no certainty that a monoclonal antibody to the overlapping region would even be raised when looking generally for monoclonal antibodies that bind to Fip-2, let alone whether it would be obvious to select for that monoclonal antibody that happens to be directed to such an overlapping region.

A monoclonal antibody, by definition, is the subject of selection. Many antibodies may be raised against Fip-2. A monoclonal antibody is a clone of only a single antibody that has been raised against Fip-2, which has been selected for its ability to bind to Fip-2. Thus, by definition, some degree of selection is required in order to obtain a monoclonal antibody that binds to Fip-2.

The present claims require that the monoclonal antibody bind RAP-2. Thus, the monoclonal antibody of the combined teachings of the prior art, selected for its capability of binding to FIP-2, must also be subject to selection for binding to RAP-2. It would not be obvious to

perform this additional degree of selection to identify those specific antibodies from among those that are capable of binding to Fip-2 that may also bind to RAP-2. Accordingly, monoclonal antibodies are one step further away from the combined teachings of the prior art than the general antibodies of claim 1. For this reason, claim 17 is unobvious from the combined teachings of the prior art in its own right as well as for the reasons discussed hereinabove for claim 1 from which it depends.

The same is true of the chimeric antibodies of claim 18. To obtain a chimeric antibody, one must start with a monoclonal antibody. Thus, the chimeric antibodies of claim 18 are independently patentable for the same reasons as discussed above for claim 17.

Accordingly, reversal of the examiner and withdrawal of this rejection specifically with respect to claims 17 and 18 are also respectfully urged.